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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/585,475	06/02/2000	N. Leigh Anderson	40488	6582

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JOHN C. ROBBINS
LARGE SCALE BIOLOGY CORPORATION
3333VACA VALLEY PARKWAY
SUITE 1000
VACAVILLE, CA 95688

EXAMINER	
WALICKA, MALGORZATA A	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 08/12/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/585,475	ANDERSON ET AL.	
	Examiner	Art Unit	
	Malgorzata A. Walicka	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08/27/04*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *85-94 and 96-105* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *85-94 and 96-105* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *See Continuation Sheet*.

Continuation of Attachment(s) 6). Other: documents used in 102 rejection.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e) was filed April 30, 2004, and Amendment to Accompany Request for continued Examination was filed July 27, 2004. Claims 1-13 and 95 were cancelled in a previous amendment; claims 14–84 have been cancelled by the instant amendment; new claims 98-105 have been added. Claims 85-94 and 95-105 are pending in the application and are the subject of this Office Action.

Office Action

1. Objections

1.1. Specification

The specification is objected to for lack of definition of the term "abundance" and "derivatization status", specification, page 7, line 31.

1.2. Claims

In the Listing of the Claims claims 1-84 and 95 are cancelled, and, simultaneously, claims 14-84 are withdrawn. The examiner understands the last is a typographical error, and treats claims 14-84 as canceled.

Objections to claims 93 and 94 made in the final rejection are withdrawn, because the claims have been corrected.

Claim 88 and 101 are objected to as comprising a grammatical error "protein markers determines". The appropriate correction is requested.

2. Rejections

2.1 35 USC, section 112, second paragraph

Claim 85-94, 96-97 and new claims 98-105 are rejected for the use of term "a degree of efficacy", or "a degree of effective response", of an agent, because neither the claims nor the specification define the term efficacy or the term effective response. As indicated in the previous Office Actions it is unknown to what word efficacy is related. Is this an efficacy of a drug in the treatment of a particular disorder? How the degree of efficacy is defined? The indefinite term and phrase render the claims indefinite.

Claim 85 recites the limitation "effective response", which is indefinite, because neither the claim nor the specification defines what the response must be effective for.

Claims 88 and 101 recite the phrase "relative amount of toxicity or effectiveness", which is confusing. Relative to what?

Claim 88 is confusing because it is not clear to what levels the claim is referring to.

Claims 96-97 and 104 recite the terms "effective amount" and "greater then effective amount", which are not defined by the claim or specification. The claims and specification do not define what the amount must be effective for.

Claim 96 recites in the second line the phrase "an amount greater than an effective amount of an agent" which is indefinite. It is not clear to what the Applicants are referring to, i.e., an amount of what?

Claims 97, 105, and 104 are also unclear because it is not known to amount of what the Applicants are referring to in the phrases "the greater amount" and "an amount greater than".

Claim 98 recites the limitation "the abundance" in the second line from the end. There is insufficient antecedent basis for this limitation in the claim, because the term "abundance" is not recited earlier in the claim. The claim recites in its preamble the term "efficacy".

In addition, it is not clear in comparison with what the abundance is significantly different. The examiner assumes, for examination purposes, the level of said marker protein is significantly different from the one observed in nontreated control or after treatment with a known effective agent.

2.2. 35 USC section 112, first paragraph

Claim 85-94 and 96-105 are rejected under 35 U.S.C. 112, first paragraph, lack of enablement for reasons made the previous Office Actions, the final rejection and paper No.10, and reiterated herein. New claims 98-105 are included in this rejection.

The specification fails to describe a degree of toxicity and/or efficacy and its measurements. The disclosure is enabling for determining changes in the presence and/or level of markers in a proteome, wherein the changes are caused by exposure of a tissue to tested chemicals. **It is not a degree toxicity or efficacy that is measured. It is the ratio of levels of the marker protein after exposure to a new chemical and a standard or untreated control that may be quantified.**

Examples presented by Applicant are silent about how to perform measurements of toxicity and efficacy, i.e. the disclosure is not enabling for a quantitative assay of toxicity/efficacy. The disclosure is enabling for visualizing the changes in the proteome induced by any agent and measuring the levels of the marker proteins. These measurements may be used further for calculating the ratio of the levels of the marker proteins after treatment with a tested drug and a standard drug or untreated control.

Applicants, themselves do not teach any standars that allow to determine whether a tested agent is toxic or efficient. Firstly, although the Applicants claim to use one or more markers from 162 markers of claims 85 and 105 or one from 107 markers from claims 86 and 99 the specification does not teach which markers should be used for measurement of toxicity and which for measurement of efficacy. Applicants attention is turned to the fact that some markes are usless in following effects of a tested drug, because they do not belong to the pathway in which said drug is metabolized. In addition, the disclosure does not teach any calibration curve that would represent **a relationship between toxic effects measured by, for example,** increased blood transaminases (see page 15, line 9) **and changes in the level of particular marker/markers in the proteome**. The disclosure also fails to teach any calibration curve for **efficacy of a drug, as for example** a relationship between the level of cholesterol in the blood after treatment with a particular drug and **a level of particular marker/markers in the proteome.**

The claimed subject matter is broad and includes unpredictable changes in the levels of proteins in the cell in response to the exposure to a drug or toxic agent. The quantity of some proteins may change in linear fashion; the amount of some proteins may be unaffected; some may disappear completely; some may change only after exposure to a certain threshold level of agent or may change in non-linear fashion. As such it would require undue experimentation to use any one or more protein markers to determine the efficiency or toxicity of a candidate agent absent guidance regarding how each marker changes in response to such agents and how the change correlate to toxicity and /or efficacy.

The specification enables one skilled in the art and the language of the claims refers to comparison of the proteome of the tissue exposed to a dose of the tested drug with that of a dose of drug for which the characteristics of proteome is already known, or with proteome for unexposed control, thus enabling quantifying the ratio of concentration of marker proteins after both exposures. However the specification is not enabling for measurements of toxicity or efficacy of a particular drug.

Claims 93-94, 96-99 and 103-105 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to a method in which the amounts of a tested agent used are

a) "pharmaceutically appropriate,

b) "effective"

b) "greater than effective",

c) "toxic".

The specification does not teaches a "pharmaceutically appropriate, "effective", "greater than effective" or "toxic" dose for any agent, neither the specification teaches how to measure such amounts (doses) so that one skilled in the art could apply them as claimed.

A skilled artisan concludes, therefore, the claimed subject matter was not described in the specification in such full, clear, concise and exact terms as to enable any person skilled in the art, to which it pertains, to use the invention.

2.3. 35 USC section 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 85-94, 96-97 and 98-105 are rejected under 35 U.S.C. 102(b) as being anticipated by Anderson at al. (A two-dimensional gel database of rat liver proteins useful in gene regulation and drug effects studies, *Electrophoresis*, **1991**, 12, 907-903)

and Anderson et al. (An updated two-dimensional gel database of rat liver proteins useful in gene regulation and drug effect studies *Electrophoresis,* **1995**, 16, 1977-1981).

The claimed invention comprises testing an agent or an antilipemic agent using display of proteome by two dimensional electrophoresis and measurements of levels of at least one marker from 162 or 107 protein markers listed in claims 85 and 98 or claims 86 and 99, wherein alternatively two control samples might be used. One of the controls is from the same tissue not treated with any agent, the other from the same tissue exposed to an agent of known toxicity or efficacy. In addition, claim 98, and dependent claims are limited to markers for which concentration in the spot in comparison with the same spot in proteome of untreated control or control treated with the known agent are significantly higher.

Anderson and her co-workers (1991) exposed liver tissue in rats to the antilipemic agents lovostatin, or lovostatin in combination with cholestyramine, or to none of the chemicals wherein the animal are on normal diet (no drug control) or on choresterol rich diet (negative control which the agent of known effects, opposite to lovostatin or lovostatin in combination with cholestyramine). The animals were sacrificed and livers removed, proteins extracted, and the levels of protein markers were measured in the liver proteome using two-dimensional electrophoresis. The claims recite 162 protein markers, 126 of which are already listed in Table 1 and 2 of Anderson 91 paper; see copies of the tables with marked positions.

As to the significance of difference of marker concentrations in the test samples and control, Anderson et al. 91 teach,

> "For each treatment, **proteins showing significant quantitative differences *vs.* appropriate controls are selected** [emphasis added] using group-wise statistical parameter (e.g., Student's t-test, Kepler procedure STUDENT). Proteins satisfying various quantitative criteria (**such as a P<0.001 difference from appropriate controls** [emphasis added]) are represented as highlighted spots onscreen or on computer-plotted protein maps and stored as spot populations", page 91, left column, second paragraph.

Thus, the limitation of claim 98-105 regarding significance of marker levels is contained in **Materials and Methods** of Anderson et al. 91.

4. Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malgorzata A. Walicka, Ph.D., whose telephone number is (571) 272-0944. The examiner can normally be reached Monday-Friday from 10:00 a.m. to 4:30 p.m.

If attempts to reach examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, Ph.D. can be reached on (571) 272-0982. The fax phone number for this Group is (571) 273-0937.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionists whose telephone number is (703) 308-0196.

Malgorzata A. Walicka, Ph.D.
Art Unit 1652
Patent Examiner

REBECCA E. PRUTY
PRIMARY EXAMINER
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